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SYSTEMATIC REVIEW AND META-ANALYSIS

A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson's disease

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AIMS

To the best of our knowledge, there are no systematic reviews or meta-analyses that compare rasagiline, selegiline and safinamide. Therefore, we aimed to perform a drug class review comparing all available monoamine oxidase type B (MAO-B) inhibitors in a multiple treatment comparison.

METHODS

We performed a systematic literature search to identify randomized controlled trials assessing the efficacy of MAO-B inhibitors in patients with Parkinson's disease. MAO-B inhibitors were evaluated either as monotherapy or in combination with levodopa or dopamine agonists. Endpoints of interest were change in the Unified Parkinson's Disease Rating Scale (UPDRS) score and serious adverse events. We estimated the relative effect of each MAO-B inhibitor versus the comparator drug by creating three networks of direct and indirect comparisons. For each of the networks, we considered a joint model.

RESULTS

The systematic literature search and study selection process identified 27 publications eligible for our three network analyses. We found the relative effects of rasagiline, safinamide and selegiline treatment given alone and compared to placebo in a model without explanatory variables to be 1.560 (1.409, 1.734), 1.449 (0.873, 2.413) and 1.532 (1.337, 1.757) respectively. We also found all MAO-B inhibitors to be efficient when given together with levodopa. When ranking the MAO-B inhibitors given in combination with levodopa, selegiline was the most effective and rasagiline was the second best.

CONCLUSIONS

All of the included MAO-B inhibitors were effective compared to placebo when given as monotherapy. Combination therapy with MAO-B inhibitors and levodopa showed that all three MAO-B inhibitors were effective compared to placebo, but selegiline was the most effective drug.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Pharmacological treatment of Parkinson's disease is based on the replacement of dopamine.
- Levodopa, dopamine agonists and MAO-B inhibitors can be used alone or in combination with each other.
- No clinical trials comparing MAO-B inhibitors actively exist and the relative effectiveness between rasagiline, selegiline and safinamide is not known.

WHAT THIS STUDY ADDS

- This analysis allowed inclusion of direct and indirect comparisons of all MAO-B inhibitors from 27 trials simultaneously.
- We estimated the relative effectiveness of all MAO-B inhibitors and ranked them according to benefit and harm.
- This approach identified selegiline as the optimal MAO-B inhibitor for pharmacological treatment of Parkinson's disease.

Introduction

Parkinson's disease is a gradually progressive neurodegenerative disease featuring reduced striatal dopamine and degeneration of dopaminergic neurons in the substantia nigra [1]. Symptoms of Parkinson's disease include typical motor symptoms like rest tremor, rigidity and bradykinesia, but many patients also experience non-motor symptoms like depression, sleep disturbance and cognitive impairment [1]. Parkinson's disease is the second most frequent neurodegenerative disease and affects 0.3% of the entire population in industrialized countries [2]. However, as Parkinson's disease is an age-related disease, the prevalence increases to about 1% in the age group above 60 years, and even up to 4% for patients over the age of 80 [2].

Pharmacological treatment of Parkinson's disease is traditionally based on the replacement of dopamine [3]. **Levodopa**, a dopamine precursor, remains the most efficacious symptomatic treatment for Parkinson's disease: however, chronic treatment with levodopa is associated with motor complications, wearing-off effect and random switches between 'on' and 'off' states [4]. Alternatives to levodopa are available, and both dopamine agonists and monoamine oxidase type B (MAO-B) inhibitors can be used alone or in combination with each other or with levodopa. However, the comparative effectiveness of these drug classes, taking account of both benefits and risks of MAO-B inhibitors and dopamine agonists in early and late Parkinson's disease, needs to be better established.

In a systematic MEDLINE search for systematic reviews involving these drugs, few studies were found. One Cochrane review investigated randomized controlled trials (RCTs) comparing MAO-B inhibitors with levodopa or dopamine agonists in early Parkinson's disease [5]. The authors included two trials in the review, both of which used **selegiline** as treatment. Their conclusion was that there was not enough evidence to support any firm recommendations regarding the routine use of MAO-B inhibitors compared to other dopaminergic drugs in early Parkinson's disease [5]. Another Cochrane review investigated RCTs that compared treatment with MAO-B inhibitors with placebo, with or without additional levodopa or dopamine agonists, in patients with early Parkinson's disease [6]. They included 12 trials in their review, 11 of which used selegiline as treatment. They found that MAO-B inhibitors delayed the need for levodopa by a few months but did not seem to delay the progression of the disease [6]. We also identified one published multiple treatment comparison (MTC) meta-analysis, which was based on a systematic review exploring placebo-controlled RCTs comparing antiparkinsonian monotherapy (levodopa, **pramipexole**, **rasagiline** or selegiline) [7]. This publication included five studies, and the authors concluded that treatment with levodopa gave the greatest reduction in UPDRS (Unified Parkinson Disease Rating Scale [8]) score compared to placebo, pramipexole, rasagiline or selegiline when used as monotherapy [7].

Most published RCTs have compared the effect of one MAO-B inhibitor against placebo, with or without additional levodopa. Very few RCTs have actively compared one MAO-B inhibitor to another or a dopamine agonist head-to-head. Since we could not find any systematic reviews or meta-analyses that compared all the available MAO-B inhibitors (rasagiline, selegiline and **safinamide**), we aimed to perform a drug class review comparing all available MAO-B inhibitors in a joint model. We based our analysis on a comprehensive literature search and pooling of data from all published clinical trials involving MAO-B inhibitors. We conducted a multiple treatment comparison meta-analysis utilizing both direct and indirect evidence along the lines of Tvete *et al.* [9], assessing which drug had the highest probability of being the most effective for early and later Parkinson's disease. In the analysis, we evaluated both clinical improvement and serious adverse events.

Methods

Literature search

We conducted a systematic literature search to identify published randomized controlled trials assessing the efficacy of MAO-B inhibitors in patients with Parkinson's disease. We searched MEDLINE, PubMed and Cochrane Central Register of Controlled Trials using the included MAO-B inhibitors (selegiline, rasagiline or safinamide) and indication (Parkinson's disease) as search terms. We limited our search to RCTs and retrieved potentially eligible publications for full-text review to determine whether they met our prespecified inclusion criteria. Publications that included men and women with Parkinson's disease aged 18 years or older, comparing the interventions of interest (selegiline, rasagiline or safinamide) to each other or to placebo, with or without additional levodopa, were eligible. We also searched through reference lists of the included trials to identify additional

trials. The literature search was conducted on 26 June 2017 and was last updated in November 2017.

The search identified 249 publications, of which 201 were excluded based on title and abstract. We found that 48 publications were eligible for full-text review. Of these, 21 were found not to be relevant for our analysis and were excluded (Appendix S1). The reasons for exclusion were: one study was not randomized, eight studies reported data on already included trials, three studies had no placebo group, one reported joint endpoint data for treatment and control groups and eight considered other endpoints. Altogether, 27 studies were included in the analysis [10–37]. Details of the study selection process can be found in the flowchart in Figure 1.

Participants and study selection

Two authors independently reviewed the full-text publications, and if both authors agreed that the publication fulfilled the pre-specified inclusion criteria, the publication was included. Publications were excluded if they did not meet the inclusion criteria concerning trial design, patient population, intervention, comparator or outcomes. We considered patients with Parkinson's disease over the age of 18, participating in a randomized, double blind clinical trial evaluating the efficacy or safety of MAO-B inhibitors either as monotherapy or in combination with levodopa or dopamine agonists. **Entacapone**, a catechol-*O*-methyltransferase (COMT) inhibitor used in combination with levodopa, was indirectly included in network 2, as it was included as a comparator treatment arm in one of the trials. We were interested in publications that examined the following endpoints; mortality, serious adverse events, dropouts or discontinuation of use, need for levodopa and change in UPDRS score. We defined responders as the number of patients with at least 20% reduction from baseline to end of study in the UPDRS score (total UPDRS score was used where this was provided, parts II and III or only part III where only these were provided), or an improvement (minimally improved, much improved or very much improved) on the Clinical Global Impression (CGI) scale [38].

Data

Table 1 displays the 27 included trials and the different drugs in the various treatment arms for each trial. The numbers of patients randomized together with the number who experienced response or a serious adverse event are given in the supplementary material (Appendix S2 and Appendix S3). Figure 2 displays the three networks of direct and indirect comparisons. In total there were 14 comparisons in network 1, 21 in network 2 and 4 in network 3 (Figure 2 and Table 1).

The disease duration was defined as short (less than three years) or long (three years or more) and dose level used was defined as low (<1 mg day^{-1} of rasagiline; <10 mg day^{-1} of selegiline; <100 mg day^{-1} of safinamide) or high, see the supplementary material (Appendix S4) for details.

Statistical analysis

For each of the networks we considered a joint model for assessing the comparable relative effects between the various MAO-B inhibitors and the comparator drug, following Tvete *et al*. [9]. In network 1 the comparator drug was placebo and

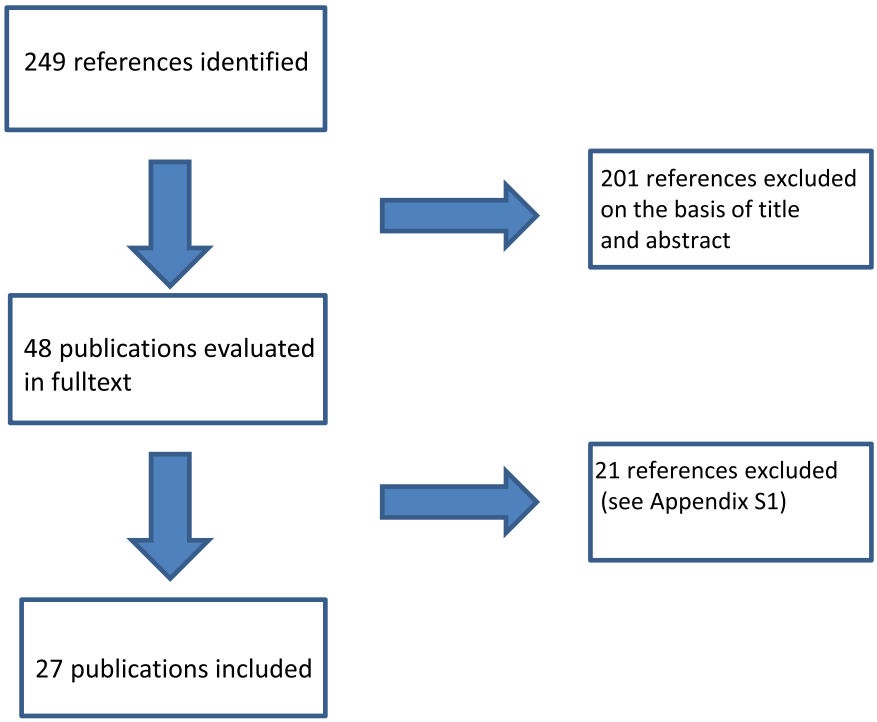

Figure 1
Identification and selection of publications

Table 1

Included studies and the different treatment arms for networks 1, 2 and 3

Network		Publication	Control	$Treat_{arm\ 1}$	$Treat_{arm\ 2}$	$Treat_{arm\ 3}$
1	1	Parkinson Study Group 2002 [10]	P	RA	RA	
	2	Stern 2004 [11]	P	RA	RA	RA
	3	Olanow 2009 [12]	P	RA	RA	
	4	Stocchi 2017 [13]	P	RA		
	5	Parkinson Study Group 1989 [14]	P	SE		
	6	Tetrud 1989 [15]	P	SE		
	7	Allain 1993 [16]	P	SE		
	8	Mally 1995 [17]	P	SE		
	9	Stocchi 2004 [18]	P	SA	SA	
2	10	Rabey 2000 [19]	PLD	RALD	RALD	RALD
	11	Parkinson Study Group 2005 [20]	PLD	RALD	RALD	
	12	Rascol 2005 [21]	PLD	RALD	ENLD	
	13	Zhang 2013 [22]	PLD	RALD		
	14	Barone 2015 [23]	PLD	RALD		
	15	Hanagasi 2011 [24]	PLD	RALD		
	16	Frakey 2017 [25]	PLD	RALD		
	17	Lim 2015 [26]	PLD	RALD		
	18	Hauser 2015 [27]	PLD	RALD		
	19	Olanow 1995 [28]	PLD	SELD		
	20	Shoulson 2002 [29]	PLD	SELD		
	21	Larsen 1999 [30]	PLD	SELD		
	22	Pålhagen 2006 [31]	PLD	SELD		
	23	Takahasi 1994 [32]	PLD	SELD		
	24	Borgohain 2014 [33, 34]	PLD	SALD	SALD	
3	25	Hauser 2014 [35]	PDA	RADA		
	26	Stocchi 2012 [36]	PDA	SADA	SADA	
	27	Schapira 2013 [37]	PDA	SADA		

DA, dopamine agonist; LD, levodopa; P, placebo; RA, rasagiline; SA, safinamide; SE, selegiline

in networks 2 and 3 it was placebo and levodopa and placebo and dopamine agonist respectively. The full statistical model is presented in the supplementary material (Appendix S5). The analyses embraced all drug treatments and comparator arms over all studies relevant for each network. Hence, all measured effects of any MAO-B inhibitor contributed to the comparison of all MAO-Bs relative to each other.

We estimated the relative effect of each MAO-B inhibitor versus the comparator drug. We examined models where the effect was dependent upon the explanatory variables disease duration or dose level, both or neither. This Bayesian approach is based on the construction of probability distributions for the parameters to be estimated, including the relative effects and the regression coefficients for the explanatory variables. Our knowledge about these parameters is uncertain, and we describe this uncertainty through probability distributions. The probability distributions describing our initial uncertainty are called prior distributions (that is, prior to examining the data). Taking into consideration the study data, the prior distributions are updated through the Bayes formula to posterior distributions.

The models were analysed in OpenBUGS [39] run from R [40]; for details, see the supplementary material (Appendix S5). From the joint model in each of the three networks, we generated samples from the posterior distribution of the relative effect of each MAO-B drug versus comparator drug and indirectly versus the other MAO-B drugs. From these posterior samples we could estimate all relevant parameters. All parameter estimates are given with a corresponding 95% uncertainty (credibility) interval. In addition, based on the samples we could estimate the probability that an MAO-B inhibitor was better than another by counting the number

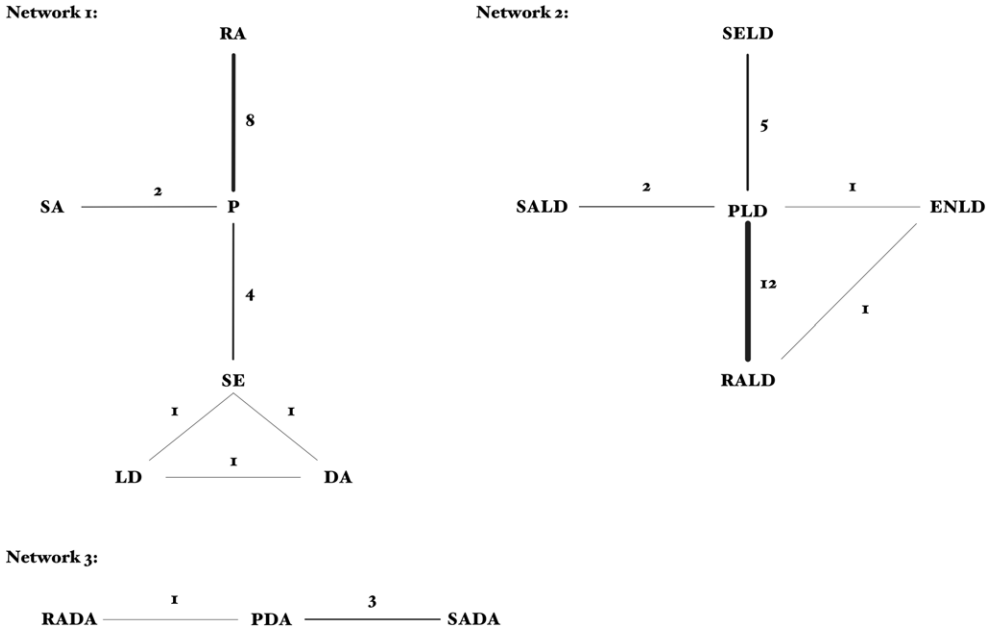

Figure 2
Overview of direct and indirect comparisons

of times the corresponding relative effect was greater. Similarly, we could estimate the probability that an MAO-B inhibitor was ranked as number 1, 2, etc.

A completely parallel model was specified for the serious adverse events (SAE) endpoint. In the SAE analyses of network 1, we omitted the Stocchi *et al.* [18] study as we ran into numerical problems in the model fitting.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [41], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.

Results

The systematic literature search and study selection process identified 27 publications eligible for our three network analyses. Overall, there were 4072 patients given MAO-B treatment, 1489 given placebo, 1457 given placebo and levodopa and 333 given placebo and dopamine agonist treatment. The patient characteristic average disease duration for a treatment arm ranged from three months to almost ten years. A total of 2937 patients had disease duration less than three years while 4641 had disease duration of three or more years. Dose level was either low (in 21 arms) or high (in 17 arms). The trials lasted between six weeks and six and a half years, most of them lasting up to 24 weeks.

We will first compare the MAO-B inhibitors with respect to their effect and thereafter we will compare them regarding the occurrence of SAEs.

Treatment effect

Network 1. When considering rasagiline, safinamide and selegiline treatment given alone and compared to placebo treatment in a model without explanatory variables, we found the relative effects to be 1.560 (1.409, 1.734), 1.449 (0.873, 2.413) and 1.532 (1.337, 1.757), respectively (Table 2 and Appendix S6). When accounting for disease duration and dose level, we found the regression coefficients for both to be non-significant. Based on the samples from the posterior distribution, we counted the number of times each MAO-B inhibitor was ranked as number 1, 2 or 3, and in Figure 3 we show histograms displaying this. Table 3 gives an overview of the probability of one drug being better than another. We found a 58% probability for rasagiline to be better than selegiline and a 68% probability for rasagiline to be better than safinamide. Similarly, there was a 65% probability for selegiline to be better than safinamide. Taken together and given the findings in Figure 3 and Table 2, there was no reason to declare one drug clearly better than another when given alone.

Network 2. For network 2, we found the regression coefficient for dose to be non-significant, while the coefficient for disease duration was significant but rather small. When considering rasagiline, safinamide, selegiline and entacapone treatment given together with levodopa compared to joint placebo and levodopa treatment in a model without explanatory variables, we found the relative effects to be 1.573 (1.369, 1.803), 1.178 (1.031, 1.350), 2.307 (1.802, 2.936) and 1.397 (1.128, 1.711), respectively (Table 2 and Appendix S6). When accounting for disease duration, the relative effects were 1.374 (1.237, 1.525), 1.311 (1.132, 1.508), 2.410 (1.874, 3.105) and 1.284 (1.048, 1.551), respectively (Table 2 and Appendix S6). That is, we

Table 2

UPDRS responders and serious adverse events in the networks; effect ratio estimates

		RA	SA	SE	
Network 1	UPDRS responders	1.560(1.409, 1.734)	1.449(0.8732, 2.413)	1.532(1.337, 1.757)	
	Serious adverse events	1.076(0.581, 1.880)	0.640(0.180, 1.219)		
		RA + LD	SA + LD	SE + LD	EN + LD
Network 2	UPDRS responders[a]	1.573(1.369, 1.803)	1.178(1.031, 1.350)	2.307(1.802, 2.936)	1.397(1.128, 1.711)
	Serious adverse events[a]	1.096(0.788, 1.540)	1.067(0.817, 1.465)	1.078(0.783, 1.592)	0.979(0.617, 1.390)
	UPDRS responders[b]	1.374(1.237, 1.525)	1.311(1.132, 1.508)	2.410(1.874, 3.105)	1.284(1.048, 1.551)
	Serious adverse events[b]	1.123(0.915, 1.450)	0.970(0.717, 1.268)	1.168(0.860, 1.843)	0.981(0.625, 1.403)
		RA + DA	SA + DA		
Network 3	UPDRS responders	1.076(0.860, 1.361)	1.191(0.994, 1.461)		
	Serious adverse events	1.274(0.561, 2.903)	1.203(0.607, 2.500)		

[a]Model without explanation variables
[b]Model with duration of disease as explanation variable
DA, dopamine agonist; LD, levodopa; RA, rasagiline; SA, safinamide; SE, selegiline

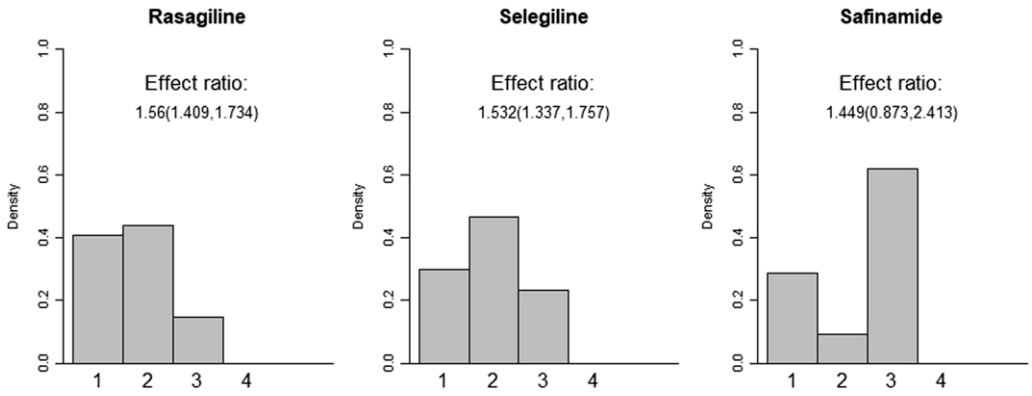

Figure 3

Histograms displaying a given MAO-B drug's effect ranked against the other drugs (ranked from left to right) when the drugs were given alone, where the height of the bars gives the probability of being ranked as number one to three. The effect ratios are the estimated effect of given MAO-B drug versus placebo treatment

found all MAO-B inhibitors and entacapone to be effective compared to placebo when given in combination with levodopa. We see that regardless of taking explanatory variables into consideration or not, selegiline is clearly more efficient than the other MAO-B inhibitors, while safinamide compares more favourably with the others when accounting for disease duration.

The ranking of the three MAO-B inhibitors and entacapone when given together with levodopa is displayed in Figure 4, both accounting for disease duration and not. Table 3 gives an overview of the probability of one drug being better than another. We found all MAO-B inhibitors and entacapone to be efficient compared to placebo when given together with levodopa. When comparing the MAO-B inhibitors given in combination with levodopa, we found selegiline to be clearly the most effective and rasagiline to be the second best. The ranking between safinamide and entacapone is switched in favour of safinamide when disease duration was accounted for, but these two drugs can be regarded as equally good and somewhat inferior to rasagiline.

Network 3. In a model without explanatory variables, both being non-significant, we found the effect ratios for rasagiline and safinamide when given together with a dopamine agonist compared to joint placebo and dopamine agonist treatment to be quite similar; 1.076 (0.860, 1.361) and 1.191 (0.994, 1.461), respectively. Notably, there was no clear difference between the two MAO-B inhibitors and placebo when given together with a dopamine agonist.

Table 3

Probabilities that one monoamine oxidase type-B inhibitor is better than another

Probability that one agent was better than another given alone			
	SE	**SA**	
RA	0.58	0.68	
SE	–	0.65	
Probability that one agent was better than another in combination with levodopa			
	RA + LD	**EN + LD**	**SA + LD**
SE + LD	1	1	1
RA + LD	–	0.9	1
EN + LD	–	–	0.91
Probability that one agent was better than another in combination with levodopa and considering duration of disease as an explanation variable			
	RA + LD	**SA + LD**	**EN + LD**
SE + LD	1	1	1
RA + LD	–	0.78	0.76
SA + LD	–	–	0.58

DA, dopamine agonist; EN, entacapone; LD, levodopa; RA, rasagiline; SA, safinamide; SE, selegiline

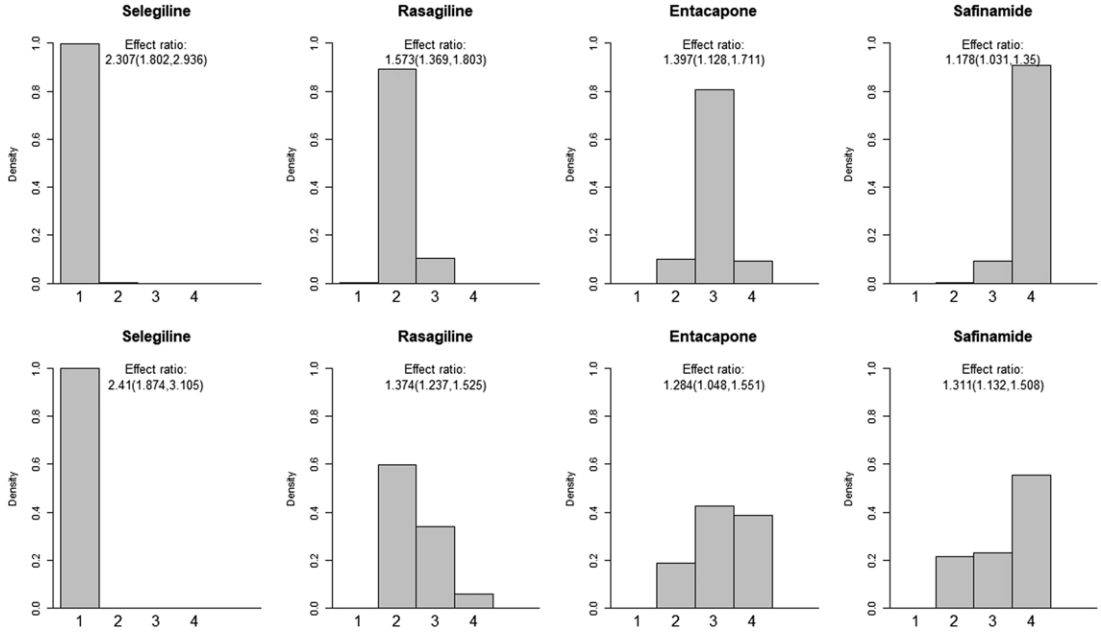

Figure 4

Histograms displaying a given MAO-B drug's effect ranked against the other drugs (ranked from left to right) when the drugs were given toghether with levodopa, where the height of the bars gives the probability of being ranked as number one to four. The effect ratios are the estimated effect of the given MAO-B drug versus placebo treatment when given together with levodopa. Top row is results when not adjusting for disease duration and bottom row is when we take disease duration into consideration

Serious adverse events

Altogether, there were few SAE events in the included studies; see Appendix S2 in the supplementary material for details. We conducted the same analyses as for the effect endpoint and found for all networks that there were no significant differences between any of the MAO-B inhibitors and comparator treatment groups with respect to SAE (Table 2 and Appendix S7). That is, when using any of the MAO-B

inhibitors, we could not find an increased risk for SAE compared to placebo or joint placebo and levodopa or dopamine agonist treatment.

Discussion

The treatment of Parkinson's disease is complex, and it is in the best interest of the patients to identify the most effective and safe treatment from a range of alternatives. The decision to start treatment with a certain drug is often made based on individual preference and clinical expertise of the treating physician. Concerning treatment with MAO-B inhibitors, we found that all of the included MAO-B inhibitors were effective compared to placebo, both when given as monotherapy and in combination with levodopa. When given as monotherapy, we found no significant difference in relative effectiveness between selegiline, rasagiline or safinamide.

When considering combination therapy with MAO-B inhibitors and levodopa, we found that all three MAO-B inhibitors and entacapone were effective compared to placebo, but selegiline was the most effective drug. When adjusting for disease duration, selegiline was still the most effective option, followed by rasagiline. One should keep these findings in mind when initiating monotherapy with a MAO-B inhibitor, as most patients with Parkinson's disease eventually will require additional treatment with levodopa. We found safinamide and entacapone to be equally effective and inferior to rasagiline, but after adjusting for disease duration, the ranking was switched in favour of safinamide, but still inferior to rasagiline. As we have not actively searched for studies examining entacapone, we cannot exclude the possibility that we are lacking evidence on this part.

Overall, there were 7578 patients included in the 27 clinical trials, and the average disease duration in the studies ranged from three months to almost ten years. When adjusting for disease duration, selegiline was still the best treatment option in combination with levodopa. Also, when we adjusted for the different dose levels, it did not alter the ranking of the drugs.

There were generally few serious adverse events reported in the included studies, and when conducting the same analyses for this endpoint as for the effect endpoint, we found no significant differences between any of the drugs. This indicates that all three MAO-B inhibitors were safe and did not have an increased risk for SAEs compared to placebo with or without levodopa/dopamine agonist.

Most of the included trials used change in the UPDRS scores as outcome measurement for clinical efficacy. We defined responders as the number of patients with at least 20% reduction in the UPDRS scores, or an improvement on the Clinical Global Impressions (CGI) scale from baseline to end of study. However, it is uncertain how much clinical difference these changes make for the individual patients, as a reduction of a few points in the UPDRS score might not have much impact on the patient's quality of life. Both the CGI scale and the Activities of Daily Living (ADL) part II of the UPDRS take this into consideration as they measure global improvement or disability in everyday life. On the other hand, not all publications included the CGI scale or the ADL part of the UPDRS in their outcome measure. Many trials focused on motor symptom improvements, for which they used the motor part of the UPDRS (part III).

Only a few previous systematic reviews have investigated the effectiveness of MAO-B inhibitors compared to placebo. A Cochrane review comparing the treatment with MAO-B inhibitors to placebo, with or without additional levodopa, found that MAO-B inhibitors improve the symptoms of Parkinson's disease and delay the need for additional levodopa by a few months [6]. They concluded, however, that the results were too weak to have major effect and that MAO-B inhibitors did not seem to delay the progression of the disease [6]. Most of the studies included in this review focused on selegiline, and hence their conclusion is primarily related to this drug.

In a recently updated review on treatment recommendations, Fox *et al*. concluded that selegiline and rasagiline improve motor symptoms and are clinically useful as treatment in early Parkinson's disease, but that they do not provide the same effect size as treatment with levodopa or dopamine agonists [42]. In contrast to our results, they also concluded that there is insufficient evidence for selegiline as an adjunct to levodopa treatment in early or stable Parkinson's disease; however, they did mention that one limitation to their review is the lack of comparison statistics to determine relative efficacy of interventions [42]. Furthermore, they found no safety concerns regarding rasagiline and selegiline, which is supported by the findings in our statistical analysis. Robakis and Fahn discussed the role of MAO-B inhibitors for Parkinson's disease, including selegiline, rasagline and safinamide in their review. In line with the other reviews, they concluded that MAO-B inhibitors may be useful in the treatment of early and mild Parkinson's disease, and that they do not provide the same antiparkinsonian effect as levodopa [43]. In a post-hoc analysis, Hauser *et al*. investigated the association between the length of exposure to MAO-B inhibitors and the degree of clinical decline in 784 patients who received an MAO-B inhibitor in the NET-PD LS1 study [44]. They found that increasing duration of MAO-B inhibitor exposure was significantly associated with less clinical decline [44].

We only identified one previous MTC meta-analysis comparing antiparkinsonian therapy. Marquez-Cruz *et al*. [7] found that patients treated with levodopa had the highest improvement on the UPDRS score (parts I–III) from baseline compared to placebo, pramipexole, rasagiline or selegiline when given as monotherapy. They also found selegiline to be the second best option, followed by pramipexole, a dopamine agonist [7]. These results are in line with our findings, which show that all three MAO-B inhibitors are superior to placebo; however, we found no significant difference in relative effectiveness between selegiline, rasagiline or safinamide when given as monotherapy. Marquez-Cruz *et al*. conducted their analysis based on only five studies, while our results are based on 27 trials.

We performed a systematic literature search which ensured that data from all relevant clinical trials were included in the MTC meta-analysis. By considering a joint model including all trials simultaneously, we were able to estimate the relative effectiveness of all MAO-B inhibitors, and hence rank them according to effect and SAEs. There

was no single trial comparing all MAO-B inhibitors actively. Our analysis allowed the inclusion of both direct and indirect comparisons of all MAO-B inhibitors from the 27 trials, making it a powerful approach. Hence, taking this approach and identifying the optimal drug may guide pharmacological treatment decisions for Parkinson's disease.

A possible weakness of any MTC meta-analysis is that the trials considered might not be comparable. Differing patient characteristics and follow-up time might potentially introduce heterogeneity in the results. An MTC regression analysis will try to capture some of the possible differences, and we have considered the impact of dose level and disease duration in this analysis. Other explanatory variables could possibly have been addressed, such as percentage of women, average patient age, trial location, publication year or more detailed information on previous patient history. However, adjusting for too many factors could exclude some studies due to lack of information, and could hence introduce selection bias.

A large, well-designed randomized controlled trial comparing all available drug interventions for Parkinson's disease would be the ideal source of data for a more detailed comparison on patient level, a 'gold-standard' comparison. Unfortunately, studies like this are not available. This demonstrates the importance of well-executed MTC meta-analyses and their ability to add valuable information to treatment guidelines. In addition, it is important to learn how the available interventions are actually used in daily clinical practice. Using nationwide registry data makes it possible to explore how these drugs are used in real life and establish comparative effectiveness.

Our analysis is based on 27 clinical trials investigating MAO-B inhibitors. We plan to extend our research to also include dopamine agonists in the future. To our knowledge, this has not been fully done, and will add further information on how the different treatment options for Parkinson's disease compare. The results from this MTC meta-analysis indicate that MAO-B inhibitors are safe and effective and can be considered in the treatment of Parkinson's disease, both as monotherapy and as an adjunct to levodopa. These findings are reassuring both for clinicians and for patients and represent the most comprehensive current available evidence base to guide shared decision making regarding MAO-B inhibitor treatment for Parkinson's disease.

Competing Interests

There are no competing interests to declare.

Contributors

C.D.B. carried out the clinical part and drafted the manuscript. I.F.T. performed the statistical analyses and drafted the manuscript. J.G. and B.N. participated in the statistical part and commented on the manuscript. M.K. was responsible for the project and participated in its planning, implementation and drafting of the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13651/suppinfo

Appendix S1 Excluded publications

Appendix S2 Overview of the total number of patients and the number with response
Appendix S3 Overview of the total number of patients and the number with SAE
Appendix S4 Overview of the dose level and disease duration in the various treatment arms
Appendix S5 The statistical model
Appendix S6 The estimated parameters for the three networks for effect endpoint
Appendix S7 The estimated parameters for the three networks for SAE endpoint